



Positive Effects of Botulinum Toxin On Patients Suffering From Depression

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ABSTRACT

Due to number of patients with depression constantly growing, new methods of treating and improving their well-being are being looked for. Depression has remained among the top diseases in terms of prevalence worldwide for years, and part of the patient group is resistant to drug treatment. Research in the area of improving the well-being of patients struggling with depression and facilitating their treatment process, such as through lifestyle changes, continues to expand. In 2006, the first publication suggesting a positive effect of botulinum toxin type A in patients suffering from depression appeared, and consistently in the following years more and more scientific papers appeared. Botulinum toxin treatments for the face are very popular; it is a drug registered for many medical indications. So what information do we have on this subject at this point? Could depression potentially become one of the indications for botulinum toxin use in the future?

Key Words: Botulinum toxin, Botulinum toxin in depression, Depression, Facial wrinkles depression, Depression syndromes, Depression lifestyle, Depression therapy, Botulinum toxin usage

INTRODUCTION

Depression is defined by the WHO as an illness characterized by a significant lowering of mood and an inability to enjoy things that previously brought joy, with accompanying feelings of sadness, emptiness and irritability. Symptoms occur for most of the day and last a minimum of 2 weeks, but also can occur over a long period of time. ¹ The number of people suffering from depression has been steadily increasing - the prevalence of depressive symptoms in adults increased from 24% between 2001 and 2010 to 37% between 2011 and 2020. As many as 34% of adolescents aged 10-19 are at risk of developing depression, and this is a higher percentage than in the population aged 18-25. Female teenagers show a higher risk of developing depression. ² Male gender is a protective factor at a young age, however as the age increases, the difference is blurred - alignment begins to occur after age of 16. ^{3,4} Additionally depression is characterized by high repetitiveness rate especially in patients with family history of major depressive disorder, recurrence 43% more likely to happen in women. ^{5,6} At the same time, the aesthetic medi-

cine market is growing at an extremely fast pace. According to ISAPS (The International Society of Aesthetic Plastic Surgery) and its report published at the 2023 congress, the aesthetic medicine market has expanded and recorded a 41.3% increase in surgical procedures performed and a 57.8% increase in non-surgical procedures in the 4 years preceding the survey. ⁷ The botulinum toxin treatments performed in order to get rid of wrinkles in the upper one-third of the face are the most commonly performed aesthetic procedures in the United States. ⁸ Botulinum toxin type A has many medical applications such as wrinkle reduction, treatment of anal fissure, migraine headaches, cervical dystonia, and overactive bladder. ⁹⁻¹³ A study was conducted on patients' satisfaction after using botulinum toxin on the face to reduce wrinkles; patients already described the first treatment as highly satisfying and having an impact on psychological well-being. ¹⁴ Lifestyle significantly influences wellbeing, and healthy habits are associated with a reduced risk of depression, and are recommended during antidepressant therapy combining psychotherapy and pharmacotherapy, especially in patients who lack an adequate response to pharmacological treatment

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alone.^{15, 16} This work aims to review previous publications on the effects of botulinum toxin applied to the facial area on the well-being of patients suffering from depression and to compare their results. In purpose to create this article, literature review was conducted. The PubMed database has been searched for keywords such as “botulinum toxin”, “botulinum

toxin in depression”, “depression”, “facial wrinkles depression”, “depression syndromes”, “depression lifestyle”, “depression therapy”, “botulinum toxin usage”. The scientific papers published to date in the PubMed database were reviewed and analyzed.

Literature review

Author	Title	Conclusion
Finzi E, Wasserman E.	Treatment of depression with botulinum toxin A: a case series.	First report of usage BT in depression case series of 10 patients After 8 weeks, 9/10 patients were not having a depressive episode, and 10 of them reported a significant improvement in their mood.
Parsaik AK, Mascarenhas SS, Hashmi A, Prokop LJ, John V, Okusaga O, Singh B.	Role of Botulinum Toxin in Depression.	Significant reduction in baseline main primary depression scores in patients compared to placebo-treated control group.
Crowley, Jiwon S. M.D.; Silverstein, Max L. B.S.; Reghunathan, Meera M.D.; Gosman, Amanda A. M.D..	Glabellar Botulinum Toxin Injection Improves Depression Scores: A Systematic Review and Meta-Analysis.	Randomized control trials that were analyzed, ended after 6 weeks with an improvement in the depressive state of patients.
Heckmann M, Teichmann B, Schroder U, Sprengelmeyer R, Ceballos-Baumann AO.	Pharmacologic denervation of frown muscles enhances baseline expression of happiness and decreases baseline expression of anger, sadness, and fear.	One possibility of mechanism of action under consideration is the relationship between emotional facial perception and the presence of depressive symptoms. The procerus and corrugator responsible for the wrinkling of the glabella region particularly affect negative perception and the emotion of anger.
Lewis MB, Bowler PJ.	Botulinum toxin cosmetic therapy correlates with a more positive mood.	12 patients underwent this therapy and 13 more underwent other aesthetic medicine treatments; patients who received botulinum toxin treatments manifested significantly more positive well-being and less anxiety and depression.
Schwartz GE, Fair PL, Salt P, Mandel MR, Klerman GL.	Facial muscle patterning to affective imagery in depressed and nondepressed subjects.	Depressed patients have significantly stronger facial expressions compared to healthy ones.
BURGEN AS, DICKENS F, ZATMAN LJ.	The action of botulinum toxin on the neuro-muscular junction.	Another potential mechanism of action seems to be to reduce amygdala activation by blocking the release of acetylcholine at synapses, since we know that its over activation is associated with experiencing negative emotions.
Qian H, Shao F, Lenahan C, Shao A and Li Y (2020)	Efficacy and Safety of Botulinum Toxin vs. Placebo in Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.	The relationship between different doses of botulinum toxin and depression, and the type of linear or non-linear association between the two, has not been established. Also gender must be further investigated since vast majority of studied are women.
Ni L, Chen H, Xu X, Sun D, Cai H, Wang L, Tang Q, Hao Y, Cao S, Hu X.	Neurocircuitry underlying the antidepressant effect of retrograde facial botulinum toxin in mice.	Studies confirms for the first time a retrograde axonal transport and cell-to-cell transcytosis from the site of botulinum toxin injection to the inner musculature of vibrissae to regulate the depressive-like phenotypes of mice

DISCUSSION

The first reports on the possible antidepressant effect of botulinum toxin appeared in 2006 - 10 patients with clinically diagnosed depression were studied and given

botulinum toxin in the glabella area. After 8 weeks, 9/10 patients were clinically assessed as not having a depressive episode, and 10 of them reported a significant improvement in their mood.¹⁷ A study by Parsik AK et al. showed a significant reduction in baseline main primary

depression scores in patients compared to placebo-treated control group (improvement and remission scores are higher by 8.3 for the group receiving botulinum toxin type A therapy, compared to 4.6 for the placebo group). This study suggests that botulinum toxin type A can cause significant improvement in depression symptoms and may provide an additional method of symptom relief for patients on antidepressant pharmacotherapy.¹⁸ An analysis of publications published between 1980 and 2020 on the possible positive effects of botulin therapy of the glabella area used to improve the mental state of patients suffering from depression showed that all of the 5 randomized control trials that were analyzed, ended after 6 weeks with an improvement in the depressive state of patients.¹⁹ Currently, the exact mechanism of action of botulinum toxin in alleviating symptoms of depression is unknown. The issue remains a topic of ongoing scientific research. One possibility under consideration is the relationship between emotional facial perception and the presence of depressive symptoms. Facial muscles influence the positive or negative perception of the face, which is closely correlated with the emotions that a particular facial expression depicts and evokes. The procerus and corrugator responsible for the wrinkling of the glabella region particularly affect negative perception and the emotion of anger. Botulin therapy of this area affects a more positive perception of the face, with a reduction in the perception of the face as sad, angry, frightened.²⁰ In order to assess the improvement in well-being after botulinum toxin therapy, 12 patients underwent this therapy and 13 more underwent other aesthetic medicine treatments; patients who received botulinum toxin treatments manifested significantly more positive well-being and less anxiety and depression.²¹ Depressed patients have significantly stronger facial expressions compared to healthy ones.²² Another potential mechanism of action seems to be to reduce amygdala activation by blocking the release of acetylcholine at synapses, since we know that its over activation is associated with experiencing negative emotions.²³ The publication by Qian H et al. notes that the relationship between different doses of botulinum toxin and depression, and the type of linear or non-linear association between the two, has not been established. The study should therefore be expanded to determine dose dependency, as well as gender, since the vast majority of those studied so far are women.²⁴ A study of the potential antidepressant effect of botulinum toxin in mice published in February 2023 confirms for the first time a retrograde axonal transport and cell-to-cell transcytosis from the site of botulinum toxin injection to the inner musculature of vibrissae to regulate the depressive-like phenotypes of mice subjected to chronic stress. Due to its limited and reversible side effects and the significant advantages of using botulinum toxin, it has potential for use in major depressive disorder.²⁵

CONCLUSIONS

Most publications indicate that the administration of botulinum toxin has a potential antidepressant effect and can support patients being treated for depression. Due to the parallel increase in the incidence of depression and the development of the aesthetic medicine market, the number of publications and studies on the possible antidepressant effect of botulinum toxin has increased in recent years, but it is important to remember that consideration of this topic requires further research, and most publications suggest the use of botulinum toxin as a supplement to standard antidepressant therapy, rather than as an exclusive treatment option. The limitations of the study include the difference in the degree of improvement between patients, the baseline stage of the disease before the study, and the predominance of women in the studies conducted to date. It is also important to keep in mind that most studies are conducted on relatively small groups of patients, which may distort the outcome, but the potential for using botulinum toxin as an additional means to treat depression, appears to be effective. In view of the current high incidence level of depression, low-invasive treatment of this type, involving a relatively low number of complications, seems to be a good supplementary treatment, especially in patients in whom pharmacotherapy and psychotherapy do not give satisfactory results. However, further research is needed to help optimize methods for potential therapy.

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